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I, KAY WARD, ACTING MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 4609 for a patent by THE UNIVERSITY OF WESTERN AUSTRALIA filed on 13 December 1999.

WITNESS my hand this
Thirteenth day of September 2000

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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

THE UNIVERSITY OF WESTERN AUSTRALIA

Invention Title:

METHODS AND DEVICES FOR OBTAINING SAMPLES FROM HOLLOW VISCERA

The invention is described in the following statement:

METHODS AND DEVICES FOR OBTAINING SAMPLES FROM HOLLOW VISCERA

Field of the Invention

The present invention relates to methods and devices for obtaining samples from hollow viscera. In particular, the present invention relates to methods and devices for obtaining samples from the gastrointestinal tract.

Background of the Invention

In order to accurately diagnose disorders such as ulcers and cancer, physicians and veterinarians often need to obtain biological samples from hollow viscera like the gastrointestinal tract. Methods for obtaining such samples have traditionally involved very expensive and invasive techniques such as gastroscopy. Gastroscopy usually requires the patient to orally receive an endoscope through the nose or mouth, which then passes through the oesophagus and into the stomach. Once in the stomach, biopsy forceps may be inserted through the endoscope such that biopsy material can be taken from the gastric mucus and/or epithelial layer of the stomach. After biopsy, the endoscope is removed from the patient. Each of the steps involved in taking a biopsy may lead to serious patient discomfort, and consequently, gastroscopy is often performed under a general anaesthesia or significant sedation. This potentially increases the problems associated with this procedure.

Accordingly, while gastroscopy has the benefit of allowing the operator to inspect the gastrointestinal mucosa, which would allow the operator to detect ulcerations and/or malignancies, such diseases are uncommon, especially in younger patients. Therefore, it would be preferable not to have to perform gastroscopy unnecessarily, and as such, there is a requirement for a procedure that is less invasive and mor cost effective.

In recent times gastroscopic examination has, to a certain degree, been replaced with less expensive and less invasive techniques such as digestible pharmaceutical capsules containing extractable strings. These extractable strings are often called gastric strings. To use, the patient holds the free end of the gastric string then swallows the capsule. The string plays out of the capsule as it travels through the patient's oesophagus until the capsule enters the patient's stomach. The capsule then either dissolves or passes through the patient's digestive system leaving the string within the stomach. After a certain period of time, the string is withdrawn and the end of the string that was in the stomach is subsequently tested for the presence of various microorganisms or gastrointestinal bleeding. Such a method and device is disclosed in US Patent No 3,528,429 and Canadian Patent No 802,858, both of which are fully incorporated herein by reference.

US Patent No 3,683,890 discloses a variation of the above device in which the outer dissolvable capsule encloses an inner capsule that is weighted with lead weight. The lead weight enables the string to drag against the inner lining of the stomach to enhance the sampling. The inner capsule is coated on the inside with silicon rubber, which collapses into a flexible bag upon disassociation of the outer capsule; the bag then passes through the pylorus of the stomach into the duodenum. When pulled from the patient, the string detaches from the bag and the bag with the weight eventually passes with the patient's stool. While this device has advantages over the system described above, the absorptive nature of the string used with this device is not large enough to collect a sufficient number of epithelial cells without dragging against the inner wall of the stomach. Moreover, the device is relatively expensive to produce because two capsules, a flexible bag and a lead weight are required.

Another prior art device has a steel ball that is

non-detachably connected to a string. The steel ball promotes the dragging of the string against the inner lining of the stomach, which enhances sampling of epithelial cells. In use, the patient swallows the capsule. When the capsule enters the stomach, it either melts, dissolves or breaks apart and passes through the digestive system. After an indwelling period, the string is pulled out of the stomach, through the oesophagus and out of the mouth. Like other prior art devices, this system has advantages. However, when the string is pulled from the stomach, the steel ball often comes into contact with the gastroesophageal sphincter. This may cause discomfort to the patient, and in some cases, can damage it. This method and device is disclosed in US Patent No. 2,773,502, the entirety of which is incorporated herein by reference.

The prior art gastric strings described above have all been used for general gastrointestinal sampling with varying degrees of success. One area for which gastric strings were hoped to be particularly useful was the detection of bacteria such as *helicobacter pylori* ("*H.pylori*"). *H.pylori* have been shown to be associated with benign gastric and duodenal ulcers, as well as gastric cancer, and these organisms tend to live under the gastric mucus and between the epithelial cells of the stomach. These types of organisms are most often heavily concentrated in lower portions (ie the antrum) of the stomach, and as such are particularly difficult to sample. Accordingly, the prior art gastric strings described above have had limited success in sampling for these organisms.

While there are other prior art diagnostics available to detect the presence of bacteria like *H.pylori*, these are not conclusive. Moreover, since these methods do not actually recover a sample of the bacterium in the stomach, it is possible the organisms being tested for will not be present, but others that these tests do react to, will be present. Accordingly, the physician often prefers

to culture the organism before prescribing antibiotic therapy.

Thus, as can be seen, there is a real requirement for an inexpensive, non-invasive diagnostic procedure that allows for the recovery of significant samples from under the gastric mucus and between the epithelial cells of the stomach, and which would be particularly useful for sampling organisms such as *H.pylori*.

One device that has recently been proposed for this purpose is disclosed in US Patent No. 5,738,110. This device includes a gelatine pharmaceutical capsule that contains a sampling string made of a mixture of bees' wax and mineral oil. The applicants of this patent contend that the sampling string used is sufficiently different to those used previously to overcome the problems highlighted above. However, one major problem that this device does not solve is the problem of bacterial contamination of the sampling string on removal from the gastrointestinal tract.

In all of the prior art devices described above, the gastric string passes through the mouth and oesophagus on withdrawal. However, none of the devices described above protect the gastric string from contamination upon its withdrawal from the stomach. This is a potential problem, as the mouth and oesophagus usually have a high background level of commensal flora, which can produce significant contamination of the string. This problem is especially relevant when trying to detect *H.pylori*, as this is a very fastidious organism that is slow to culture. Consequently, commensal organisms which contaminate the string often outgrow the *H.pylori* in culture to such a degree that detection of *H.pylori* is difficult if not impossible.

Thus, based upon the foregoing, it would be readily apparent to those of skill that there is a need for a relatively inexpensive gastrointestinal sampling device that enhances sampling without contributing to the discomfort of the patient. Moreover, there is a

requirement for a device that is capable of sampling microorganisms from specific regions of the gastrointestinal tract without becoming contaminated with microorganisms from other regions. Accordingly, the present invention attempts to overcome or at least alleviate some of the problems highlighted above especially those related to the contamination problems discussed.

Summary of the Invention

The present invention is directed towards a gastrointestinal sampling device that increases the number of epithelial cells removed from the stomach lining without causing additional discomfort to the patient, and which is particularly useful for obtaining samples from under the gastric mucus and between the epithelial cells of the stomach. To these ends, the present invention provides a gastrointestinal sampling device comprising:

a drag material for obtaining a gastrointestinal sample; and

a protective sheath for deployment about the drag material such that the drag material is substantially enclosed by the protective sheath upon removal from the gastrointestinal tract.

The present invention further provides a gastrointestinal sampling device for the diagnosis of certain gastrointestinal pathogens comprising:

a drag material for obtaining a gastrointestinal sample; and

a protective sheath for deployment about the drag material such that the drag material is substantially enclosed by the protective sheath upon removal from the gastrointestinal tract.

The present invention further provides a method of gastrointestinal sampling comprising the steps of:

swallowing a gastrointestinal sampling device comprising a drag material and protective sheath;

allowing sufficient time for said drag material

to obtain said gastrointestinal sample;

withdrawing said drag material such that on withdrawal said protective sheath encloses said drag material; and

recovering said gastrointestinal sample for testing.

Preferably, the gastrointestinal sampling device further includes a capsule for carrying the drag material and protective sheath.

Preferably, the protective sheath is deployed about the drag material by movement from the retracted position to an extended position. Preferably, the retracted position of the protective sheath is held in place by edible glue.

Preferably, the drag material is folded within the capsule, and has a weight for assisting with the extension of the drag material in the stomach of a patient.

The present invention further provides a method of manufacturing a gastrointestinal sampling device comprising the step of encasing a drag material and protective sheath in a capsule.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", means "including but not limited to" and is not intended to exclude other additives, components, integers or steps.

Brief Description of the Drawings

Figure 1 is a front side view of the gastrointestinal sampling device.

Figure 2 is a diagrammatic view of the protective sheath in extended form.

Figure 3 is a diagrammatic representation of the device in use. Panel A shows the device in situ in the stomach before the capsule dissolves. Panel B shows the capsule dissolved, the drag material deployed and the protective sheath retracted. Panel C shows the device

being removed with the protective sheath deployed such that it encases the drag material.

Detailed Description of the Invention

Without affecting the generality of the invention described above, the present invention will now be described with reference to the accompanying drawings.

Figure 1 illustrates a device according to one embodiment of the present invention. A gastrointestinal sampling device 10 includes a capsule 14. The capsule 14 can be of any size. Preferably, the capsule 14 is no more than 2 cm in length and 0.9 cm in diameter. More preferably, the capsule 14 is between size 00 and size 000 ie a size that a patient could easily swallow. The capsule 14 contains drag material 12, which comprises two portions 12a and 12b.

Capsule 14 may or may not be dissolvable, and may comprise more than one piece or part. If the capsule 14 is dissolvable, it is preferable that it is constructed of gelatine or other pharmaceutically acceptable material that readily dissolves when subjected to stomach acid. If the capsule 14 is constructed of non-dissolvable material, it is preferable that the material used is either plastic or some other non-toxic material, which will readily pass through the digestive system. Furthermore, if the capsule is non-dissolvable it is preferable that it is composed of at least two parts joined together with water-soluble glue. As described in more detail below, this construction will allow the capsule to separate *in vivo* such that the drag material 12 is released.

The gelatine capsule 14 may be substituted with a hot gelatine dip, which encases sterilised drag material 12. When the gelatine cools, the drag material 12 can be formed as a capsule surrounded by gelatine. The gelatine used for the hand dipped capsule embodiment of the device 10 may be softer than the gelatine used in standard gelatine pharmaceutical capsules.

The portion 12b is preferably situated adjacent to one end of the capsule 14. Both portions of drag material 12 may be composed of the same material for their entire lengths, or alternatively, portions 12a and 12b are made of different material(s). Whether different material is used for both portions or not, it is preferable that at least portion 12b is malleable, yet firm enough to maintain its mass against moderate resistance. Accordingly, portion 12b may be composed of any material which fits this description; however, it is preferable that it is composed of material selected from the group consisting of absorbent string, sampling cloth, steel wool and chain link material or a combination thereof. Most preferably, the drag material 12 *per se* or portion 12b is absorbent string such as nylon or cotton string.

The lengths of portion 12a and 12b will depend upon the size of the individual or animal being tested, as well as the sample site. Preferably, portion 12b is at least 12 cm in length.

In one preferred embodiment, portion 12b is a malleable sampling material such as absorbent string or sampling cloth, while portion 12a is either absorbent string or like material. Portion 12a runs through an opening or perforation 20 in the capsule 14, while portion 12b is located within one end of the capsule 14. As shown in Figure 1, the majority of portion 12a runs through the opening or perforation 20, while the rest of portion 12a is inside capsule 14 and attached to portion 12b. Portion 12b is tightly wound or randomly packed in cocoon-like fashion within capsule 14.

In another preferred embodiment, portion 12b is wound such that a weight 16 at the end of portion 12b is located on the exterior of the winding. Such an arrangement allows for portion 12b to be pulled out of the capsule 14 without binding or snagging. Portion 12b can also be installed in the capsule 14 by randomly packing within the capsule 14. Further, portion 12b can also be

installed in capsule 14 by packing it within the capsule in accordion-like fashion.

Surrounding portion 12b, and the segment of portion 12a that is inside capsule 14, is a protective sheath 22. The protective sheath 22 may be made of any suitable material known, including plastic, cloth or finely knitted metal. Preferably, the protective sheath 22 is plastic, and made from either polyethylene or polythene film. Protective sheath 22 may also be of any length or diameter, but generally depends upon the size of portion 12b used. For example, the sample site in the gastrointestinal tract will dictate the length of portions 12a and 12b required. As the role of protective sheath 22 is to cover the majority of portion 12b on withdrawal, it must be of sufficient length to accomplish this. Preferably, protective sheath 22 is approximately 10 cm long.

In Figure 1, protective sheath 22 is shown concertinaed in one end of capsule 14 with portion 12b tightly wound or randomly packed in cocoon-like fashion. Protective sheath 22 is preferably an open-ended tube, wherein the open end 26 is distal to the hole or perforation 20 in the end of capsule 14. The closed end of protective sheath 22 is in close proximity to, or in contact with, the region of capsule 14 which contains the hole or perforation 20. In this configuration, portion 12a passes through the protective sheath 22 as depicted in Figure 1. In order to stop portion 12b being pulled through the hole or perforation 20 upon withdrawal or during swallowing, it is preferable to have a protective sheath retainer 24 present. The protective sheath retainer 24 may be a simple knot in portion 12b, or it may be any other means by which the passage of portion 12b through the protective sheath 22 can be stopped. For example, protective sheath retainer 24 may be a small plastic or metallic bead.

As shown in Figure 1, the terminal end of portion

12b, ie the end not attached to portion 12a, is preferably attached to a weight 16. The weight 16 can be permanently or detachably fixed to portion 12b. Weight 16 may be constructed of any suitable material, and be of any suitable size. The role of weight 16 in use is to assist in the deployment of portion 12b once capsule 14 dissolves or separates. Preferable, the weight 16 is made of non-toxic metal as in use it may be desirable to increase the effectiveness of the sampling by applying a magnetic force to the weight 16 to position it as required.

As described in more detail below, it is preferable that in use the protective sheath 22 does not deploy at the same time as portion 12b. In order to effect this it is preferable that protective sheath 22 is halted in its deployment for a period of time considered sufficient to allow portion 12b to extend, and come into contact with the sample site. A person skilled in the art will appreciate the significance of this time delay, as well as be able to determine what the period of time should be. In one preferred embodiment, this delay in deployment is effected with the use of glue 18. A bead of glue 18 is attached to the protective sheath 22 such that protective sheath 22 can not expend to its complete length for approximately 10 minutes after the capsule 14 has dissolved or separated. Preferably, glue 18 is water-soluble glue that is non-toxic and edible.

Figure 2 depicts the device of Figure 1 in fully deployed form, illustrating the protective sheath 22 in greater detail.

In one preferred embodiment of the preferred invention, the length of portion 12b is increased and the width is decreased such that the same volume of material fits within the capsule 14. Thus, for example, instead of using a length of 20cm and a width of 2 cm for portion 12b, the length of portion 12b would be 40cm and the width would be 1cm. The advantage of an elongated portion 12b is that it is better able to collect and facilitate detection of

any bleeding that might occur within the entire length of the stomach including the gastro oesophageal junction.

One especially preferred embodiment of the present invention is depicted in Figure 3, and is shown as it is intended to be used. The capsule 14 is constructed from gelatine. A fasting patient swallows the capsule 14 with a drink of water. Preferably warm water is used. As the capsule 14 is swallowed it pulls drag material 12a down the oesophagus into the stomach with it. Within approximately 5 minutes of entering the stomach, the warm moist environment causes the capsule 14 to dissolve. At that time, by its own weight, or by the action of the weight 16 and by posturing the patient, portion 12b deploys from the protective sheath 22 and unrolls 12 to 15 cm within the stomach. At this time, because the protective sheath 22 is held in place by water-soluble glue 18 it does not deploy. The patient remains in the vertical position while portion 12b deploys and comes into intimate contact with the adjacent mucus lining of the stomach. Contact with the mucus layer can be enhance by applying a magnet to the abdomen, thus pulling portion 12b or weight 16 composed of a magnetic substance tightly against the gastric mucosa. Portion 12b then collects mucus from the gastric wall and remains in this position for up to one hour. The mucus contains many *H.pylori* organisms. Other organisms, which might have been swallowed with a capsule 14, are by now killed by the gastric acid present in the stomach. During this time also, the drink of water, which was taken with the capsule 14, has passed into the intestine. Accordingly, the stomach is rather dry with both adjacent walls in contact with portion 12b, thus loading it with mucus. After a suitable time portion 12b is withdrawn by pulling on portion 12a which still protrudes from the mouth. As portion 12b is retrieved, friction against the gastric walls and against the lower oesophageal sphinter 28 causes the protective sheath 22 to fully deploy, while portion 12b is held in place such that the protective

sheath 22 envelops it

Accordingly, as the protective sheath 22 and portion 12b are retrieved through the oesophagus, the mucus laden portion 12b is enclosed within the protective sheath 22 with the open end of the protective sheath 26 distally near the weight 16. Upon retrieving portion 12b, the ends of the protective sheath 22 are clamped thus sealing the gastric mucus and portion 12b within the protective sheath 22. The external parts of the protective sheath 22 can then washed before it is opened, portion 12b retrieved and cultured in the normal fashion for gastric mucosal biopsy or mucus specimen. Alternatively, a needle and syringe could be used to pierce the protective sheath 22, irrigate the inside with sterile saline, and aspirate the resuspended material with subsequent spinning and culture.

In a further preferred embodiment, the capsule 14 is placed in the end of a tube 30, for example a large polythene drinking tube or straw, and the drag material 12 is laid in the tube 30 behind the capsule 14 with 30cm of the drag material 12 removed from the capsule 14. This is depicted in Figure 4. It is evident from this design that there is no need for the drag material 12 to actually be rolled up inside the capsule 14 except for the piece which needs to open up inside the stomach. The end of the tube 30 away from the patient's mouth has a slit 32 into which the drag material 12 can be placed and held by tying a knot.

In Figure 4 it can be seen that, in use, the tube has two ends, namely, a "drag material end" 34 and a "capsule end" 36. To swallow the capsule 14 after it has been loaded into the tube 30, the drag material end 34 is placed into a suitable drink, for instance a slightly acidic fruit juice drink or a carbonated drink, and the patient places the capsule end 36 of the tube 30 into his/her mouth. The patient then drinks the beverage in the normal fashion, during which time the capsule 14 is sucked from the end of the tube 30 with the column of liquid and

ingested with minimal fuss. The device then operates in a similar fashion to that already described above.

Dated this 13th day of December 1999

THE UNIVERSITY OF WESTERN AUSTRALIA

By their Patent Attorneys

GRIFFITH HACK

Fellows Institute of Patent and

Trade Mark Attorneys of Australia

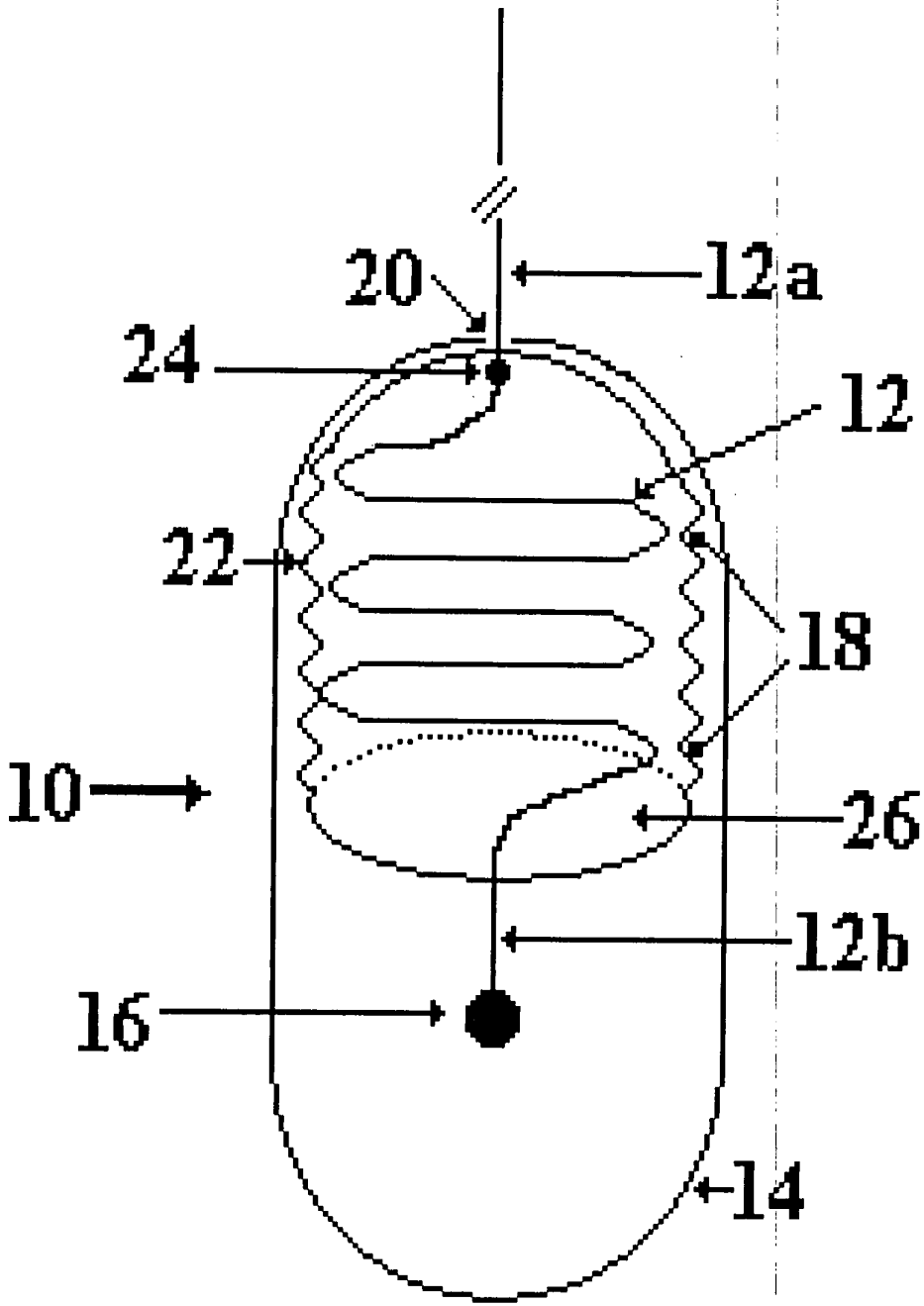

FIGURE 1

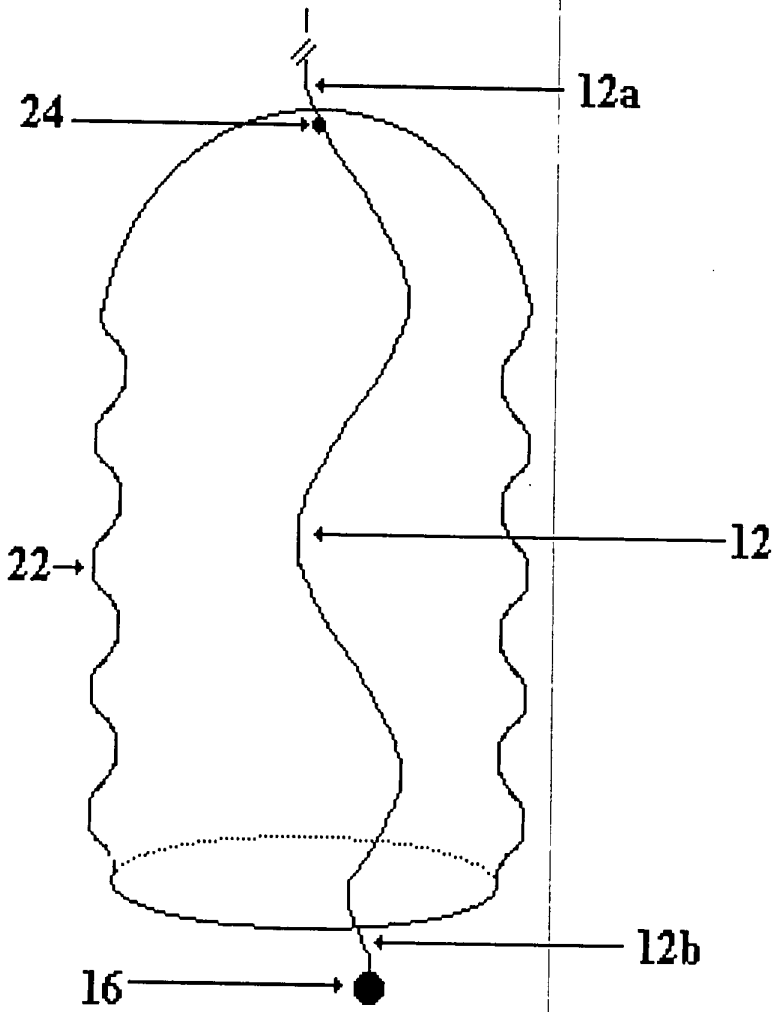

FIGURE 2

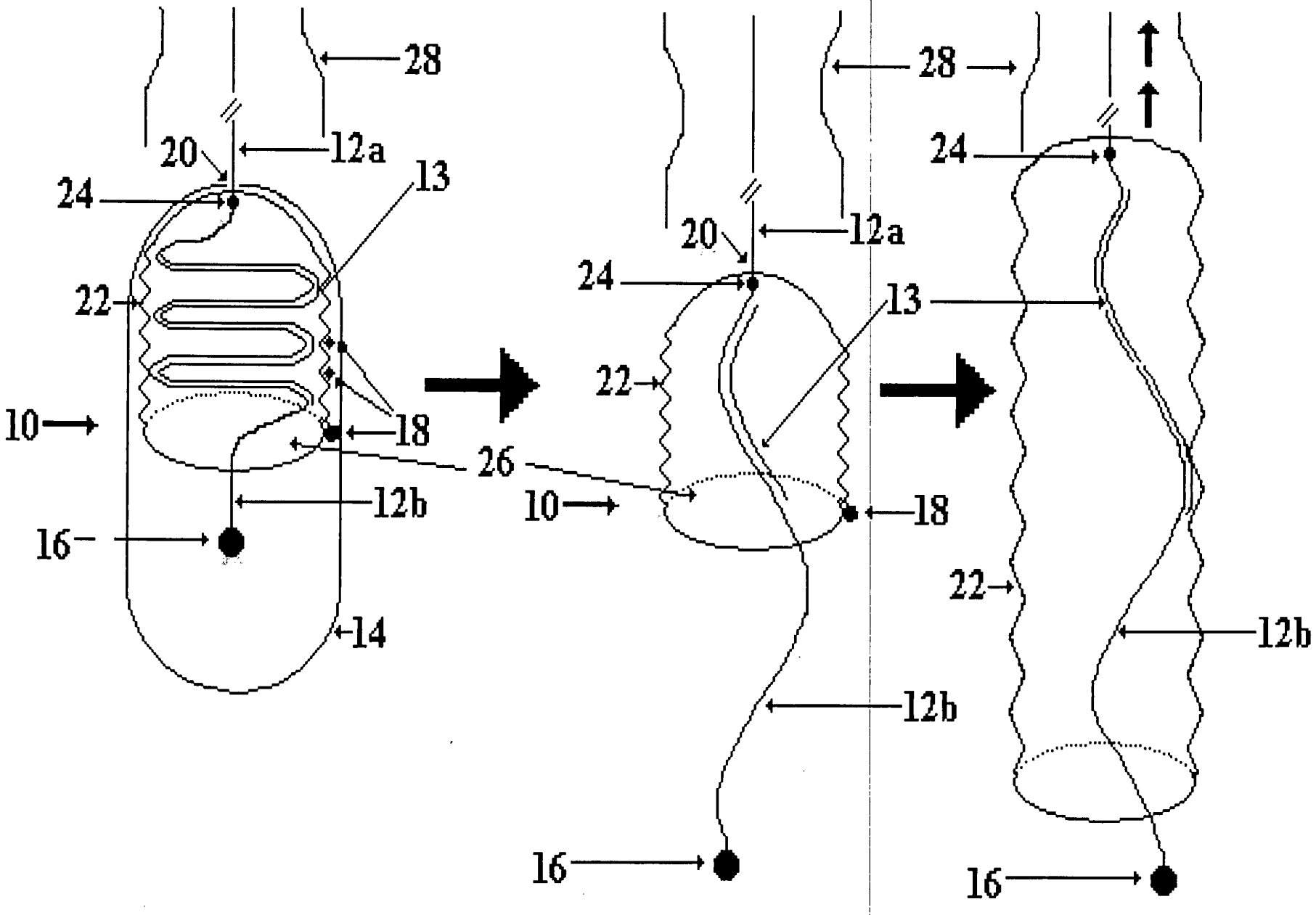

FIGURE 3

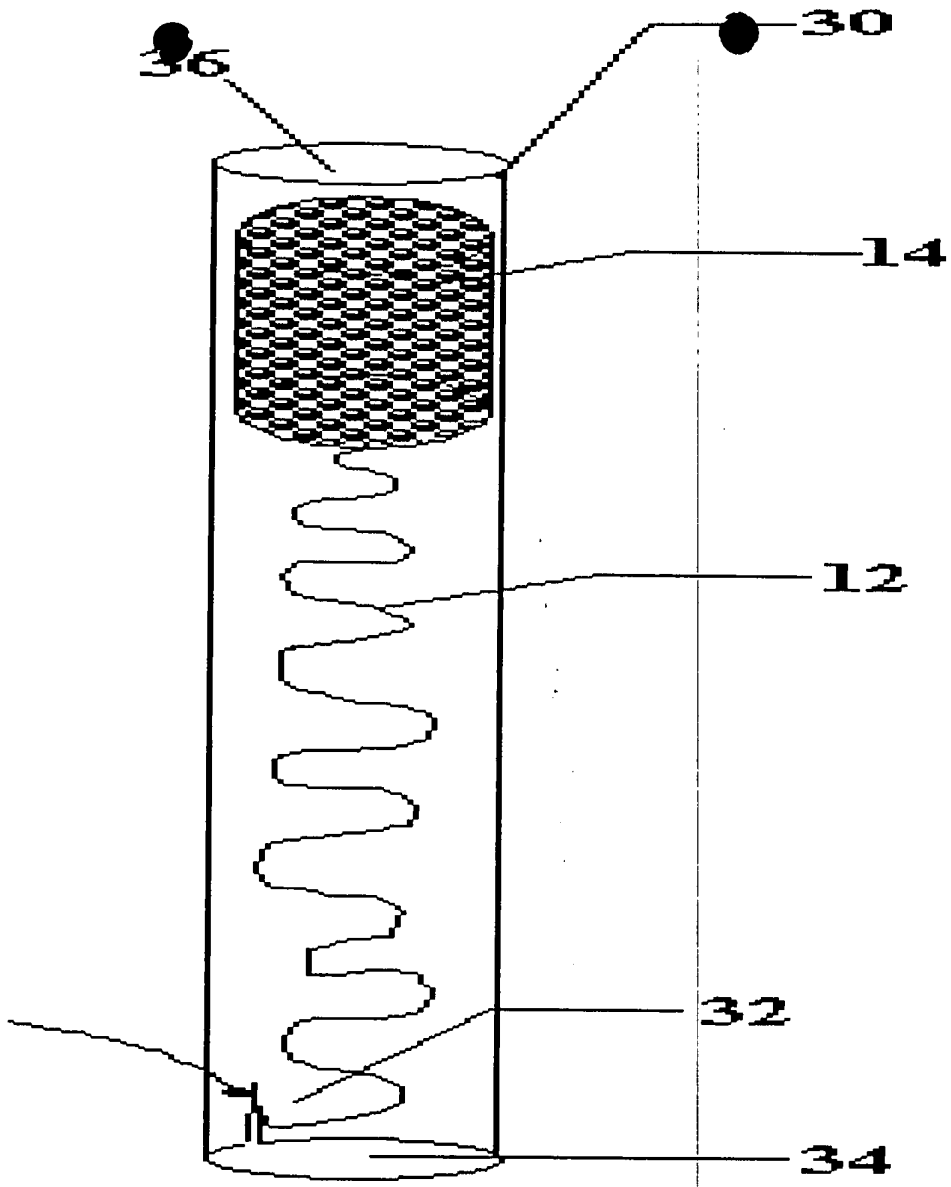

FIGURE 4